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Nuclear Receptors as Therapeutic Targets for Neurodegenerative Diseases: Lost in Translation

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Abstract

Neurodegenerative diseases are characterized by a progressive loss of neurons that leads to a broad range of disabilities, including severe cognitive decline and motor impairment, for which there are no effective therapies. Several lines of evidence support a putative therapeutic role of nuclear receptors (NRs) in these types of disorders. NRs are ligand-activated transcription factors that regulate the expression of a wide range of genes linked to metabolism and inflammation. Although the activation of NRs in animal models of neurodegenerative disease exhibits promising results, the translation of this strategy to clinical practice has been unsuccessful. In this review we discuss the role of NRs in neurodegenerative diseases in light of preclinical and clinical studies, as well as new findings derived from the analysis of transcriptomic databases from humans and animal models. We discuss the failure in the translation of NR-based therapeutic approaches and consider alternative and novel research avenues in the development of effective therapies for neurodegenerative diseases.

Keywords

nuclear receptors; neurodegenerative diseases; Alzheimer's disease; Parkinson's disease; Huntington's disease; amyotrophic lateral sclerosis

1. INTRODUCTION

Neurodegenerative diseases are characterized by progressive neuronal loss that leads to a broad range of clinical manifestations typically associated with severe motor disability, cognitive decline, and dementia. Currently, more than 40 million people worldwide are affected by these disorders, and since age is the major risk factor for most neurodegenerative diseases, the aging of the global population will further increase the burden of these disorders (1). Available therapeutic strategies are limited and mainly focus on symptomatology, as they are not able to delay the underlying progressive loss of neurons. Therefore, the development of novel and effective therapies to treat these diseases is urgent.

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Several lines of evidence have established an association between neurodegenerative diseases and type II nuclear receptors (NRs), namely the retinoid X receptor (RXR), the retinoic acid receptor (RAR), the liver X receptor (LXR), the peroxisome proliferator-activated receptors (PPARs), and, more recently, the nuclear receptor related-1 protein (Nurr1) (2, 3). NRs belong to a superfamily of ligand-activated transcription factors that regulate the expression of a wide range of genes. In general, NR activity modulates energy and lipid homeostasis in response to environmental and dietary changes (4). Over the past two decades, a myriad of studies have built a robust body of evidence showing that the activation of NRs in animal models of neurodegenerative diseases exerts salutary effects (3). However, the translation of this strategy to human patients has been unsuccessful in several clinical trials that have failed to show therapeutic efficacy. Given the promising preclinical results, it remains unclear why the clinical translation of NR activation has been unsuccessful. In this review, we summarize the role of NRs in neurodegenerative diseases, considering both preclinical and clinical data. Our objectives are to better understand the reasons for failure in the translation of this therapeutic strategy and to suggest alternative research avenues, in the context of NR signaling, that could have a better chance to succeed in patients suffering from these diseases.

1.1. Neurodegenerative Diseases

Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are among the most prevalent neurodegenerative diseases. These disorders exhibit a marked neuroinflammatory component and are predominantly associated with the abnormal accumulation of proteins such as β -amyloid ($A\beta$), microtubule-associated protein tau, α -synuclein (α -syn), huntingtin (htt), superoxide dismutase 1 (SOD1), and TDP43.

1.1.1. Alzheimer's disease.—AD is characterized by the accumulation of $A\beta$ peptides generated from the sequential cleavage of amyloid precursor protein (APP) by β and γ secretases, giving rise to mainly $A\beta$ peptides that are either 40 or 42 amino acids in length. The self-aggregating $A\beta_{42}$ peptide drives the generation of oligomeric species, which ultimately results in $A\beta$ deposition in the brain parenchyma where they form amyloid plaques (5, 6). The accumulation of amyloid peptides and deposits leads to neuroinflammatory processes, hyperphosphorylation of the tau protein (p-tau), and subsequent neurodegeneration (5). Although the majority of AD patients exhibit the sporadic, late-onset disease, thought to be due to the impairment of $A\beta$ clearance mechanisms, a subset of patients inherit familial AD, which is due to genetic variants that favor the generation of $A\beta_{1-42}$ species (5, 7).

1.1.2. Parkinson's disease.—The predominant form of PD is sporadic with only about 10% of cases being inherited (8). Traditionally, PD has been diagnosed based on the presence of Lewy bodies composed of misfolded and/or aggregated forms of the protein α -syn, which is associated with the progressive loss of vulnerable dopaminergic neurons, primarily in the substantia nigra. Specific point mutations in the α -syn gene, *SNCA*, as well as *SNCA* multiplications, have been linked to inherited forms of PD (9). Along with protein

misfolding, several other pathological mechanisms seem to underlie PD pathology, such as mitochondrial dysfunction, endoplasmic reticulum (ER) stress, aberrant ubiquitin, and chaperon-mediated autophagy clearance (10, 11).

1.1.3. Huntington's disease.—HD is a rare inherited autosomal-dominant disorder that results from the presence of expanded CAG repeats in the gene encoding htt. The CAG repeats give rise to mutant forms of htt (mhtt) harboring a polyglutamine (polyQ) domain, which induces conformational changes, resulting in intracellular aggregates (12). Although the exact mechanisms by which intracellular polyQ-htt aggregates cause neuronal death remain unclear, it has been suggested that transcriptional deregulation due to sequestration of critical transcription factors, such as p53, SP1, and CBP, by intracellular mhtt aggregates might play an important role (13).

1.1.4. Amyotrophic lateral sclerosis.—ALS is characterized by the degeneration of large motor neurons in the brain and spinalcord, and has a multifaceted etiology that includes impaired messenger RNA (mRNA) stability and microRNA processing; altered axonal trafficking of mRNA; dysregulated transcription due to mutations in genes such as *TDP43*, *FUS*, and *C9ORF72*; glutamate mediated excitotoxicity; and impaired neurotransmitter release (14). Additionally, mutations in the *SOD1* gene, including G93A, result in the misfolding and aggregation of the mutant SOD1 protein within motor neurons, which leads to ER stress, mitochondrial dysfunction, and further disruption of axonal transport, which in turn results in neuronal loss. Similar to HD, neurodegeneration in ALS is also associated with dysregulated transport of ubiquitinated proteins to the proteasome and impaired proteasome/autophagosome functions (14, 15).

1.2. Nuclear Receptors

The type II NRs compose a family of ligand-activated transcription factors that form obligate heterodimers with RXR. The dimeric receptor binds to sequence-specific DNA response elements that are positioned in the enhancer and promoter regions of their target genes, and act to directly regulate gene transcription (16) (Figure 1). Importantly, NR heterodimers can be considered permissive when the heterodimer is activated by ligation of either member of the receptor pair, and when it is simultaneously ligated, it can respond in an additive or synergistic fashion. This is the case for LXR, PPAR, and Nurr1 heterodimers with RXR. On the other hand, heterodimers of RAR with RXR are considered to be conditionally permissive since it is the binding of a RAR ligand that activates the dimer and subsequently allows the binding of RXR ligands, which increases the transcriptional potential of RAR. This type of heterodimer is not activated by RXR ligands alone; there are also nonpermissive RXR heterodimers, such as the thyroid hormone receptor, which respond only to ligands of the nonpermissive binding partner and not RXR (17, 18). In the absence of ligand binding, RXR heterodimers are bound to DNA and inhibit transcription through their interaction with corepressor complexes (16, 18, 19). Interestingly, monomers of PPAR γ , LXRs, and Nurr1 are also able to repress gene expression, namely of nuclear factor- κ B (NF- κ B) target genes, which inhibit the inflammatory response (19, 20).

1.2.1. RXR.—The three RXR isoforms RXR α , RXR β , and RXR γ , are expressed in several regions of the adult brain in sex- and isoform-specific patterns (21, 22). The roles of RXRs are very diverse owing to their ability to dimerize with other type II NRs, activating many different genes and pathways. Although 9-*cis*-retinoic acid was initially proposed to be the endogenous ligand for RXR, several inconsistencies have raised doubts about this assumption, and the primary endogenous or natural ligands for these receptors remain unclear. Finally, n-3 polyunsaturated fatty acids (PUFAs), such as docosahexaenoic acid, have been identified as RXR ligands, as have 9-*cis*-13,14-dihydroretinoic acid, and phytanic acid (23, 24).

1.2.2. RAR.—Similar to RXR, the three RAR isoforms, RAR α , RAR β , and RAR γ , are expressed throughout the adult brain in sex- and isoform-dependent, region-specific patterns (21, 22). RARs bind to all-*trans*-retinoic acid (RA), which serves as its principal ligand, but also interact with 9-*cis*-retinoic acid (25). Mice lacking RAR β exhibit impaired long-term depression and long-term potentiation of synaptic transmission (26), and the knockout of RAR α in mice revealed that this receptor is required for the homeostatic synaptic plasticity, i.e., the ability of neurons to adjust their own excitability to maintain the stability of circuit activity, mediated by RA (27). Aside from their role in cognition, RARs also seem to play a role in motor function in coordination with RXR (25). It has also been suggested that RARs are important regulators of sleep and the circadian cycle (28).

1.2.3. LXR.—Although both LXR isoforms, LXR α and LXR β , are expressed in the brain, LXR β exhibits a more extensive expression pattern in this organ (29). LXRs regulate lipid homeostasis and inflammation and are activated by endogenous oxysterols derived from cholesterol. The critical role of LXR in the brain is demonstrated by genetic models lacking these receptors. LXR double-knockout mice exhibit several brain abnormalities, including excessive lipid deposition, astrogliosis, and extensive neuronal loss (30). LXR β -specific knockout mice also exhibit lipid accumulation, motor neuron degeneration, and astrocytic proliferation (31).

1.2.4. PPARs.—The three PPAR isoforms, PPAR α , PPAR β/δ , and PPAR γ , are expressed throughout the brain, and it seems that PPARs are more highly expressed in neurons than in other cell types (32). Endogenous and natural ligands of PPARs include mainly PUFAs and their derivatives, as well as other lipids (33). PPAR γ has an important role in the anti-inflammatory response, neuroprotection, and neuronal differentiation and function (34, 35). PPAR α has been linked to neuroprotection and anti-inflammatory responses (36), as well as to the regulation of energy homeostasis (37) and synaptic function (38). Finally, PPAR β/δ is involved in astroglial and oligodendrocyte differentiation, myelination, and neuroprotection (39).

1.2.5. Nurr1.—Nurr1 is a member of the NR4A family, and, unlike type II receptors, it can directly bind to DNA and regulate transcription as a monomer or homodimer, or as a heterodimer with RXR (40). Nurr1 is expressed at high levels in the brain (41), and studies using Nurr1 knockout and conditional knockout mice have established the critical role of

Nurr1 in the generation and development of dopaminergic neurons as well as in the maintenance and survival of these cells (42–44). It is still not clear whether Nurr1 interacts with an endogenous or natural ligand; however, the transcriptional activity of the Nurr1:RXR heterodimer can be stimulated by ligands interacting with RXR (45).

2. THE ROLE OF NUCLEAR RECEPTORS IN NEURODEGENERATIVE DISEASES

Although the therapeutic role of NRs in neurodegenerative diseases has been extensively characterized by numerous studies using different animal models and ligands, NR agonists have generally failed to demonstrate clinical efficacy. In this section, we review preclinical evidence for a neuroprotective role of NR activation in different animal models (summarized in Table 1), systematize crucial mechanisms underlying their effects (Figure 2), and summarize the clinical outcomes arising from this therapeutic strategy (Table 1). We also review studies and analyze transcriptomic databases containing data from the central nervous system of human patients to better understand the role of NRs in these pathologies. The expression profile of NRs as well as the levels of endogenous or natural ligands observed in these patients is summarized in Table 2.

2.1. RXR in Alzheimer's Disease

RXR α mRNA and protein expression levels are increased in the brains of AD patients (Table 2), which is evident at very early stages of dementia in the temporal gyrus and hippocampus and persists throughout the disease (46). The analysis of global gene expression in neurons obtained from several areas in the brains of AD patients indicates that the neuronal expression of RXR α is not altered (Table 2), suggesting that the increase in RXR α expression is likely to occur in non-neuronal cells. The RXR agonist bexarotene was initially described to increase astrocytic apolipoprotein E (ApoE) expression and ApoE-mediated A β clearance, as it rapidly lowered brain A β burden and rescued cognitive deficits in the AD mouse model APP/PS1 (47). Although subsequent reports using bexarotene and LG100268, another RXR agonist, did not fully recapitulate these first findings with respect to plaque clearance, many of the beneficial effects have been reproduced in different studies (48, 49). RXR activation induces ApoE and ABCA1 expression, leading to an increase in ABCA1-mediated lipidation of ApoE and high-density lipoprotein (HDL) levels in the brain. ApoE-containing HDLs were shown to stimulate the proteolytic degradation of A β through microglial neprilysin and extracellular insulin-degrading enzyme (47, 50). It has been found that RXR activation by bexarotene induces A β phagocytosis by brain myeloid cells, which is associated with an increase in the expression of the phagocytic receptors MerTK, Axl, and Trem2 (51, 52). Bexarotene has also demonstrated direct neuroprotective effects in the AD mouse model 5xFAD, where it repressed inflammation, prevented neuronal loss, and was accompanied by an increase in synaptic markers and behavioral improvement (53). Although bexarotene has shown great therapeutic potential for AD in several animal models, its performance in clinical trials has been disappointing as it penetrates the blood-brain barrier poorly and elicits serious side effects, including hypertriglyceridemia (54). In a small clinical trial, however, AD patients with ApoE3 alleles experienced significant reduction in amyloid burden within 30 days of the start of treatment (55).

2.2. RXR in Parkinson's Disease

The available data indicate that there is a decrease in RXR α mRNA expression in the dopaminergic neurons of PD patients (Table 2). In 2013, a large screen of possible Nurr1/RXR ligands found that bexarotene preferentially bound to the Nurr1/RXR heterodimer. A low dose of bexarotene significantly protected dopamine neurons in the substantia nigra of the 6-hydroxydopamine (6OHDA) rat PD model, suggesting that low oral doses of bexarotene might provide an effective and well-tolerated therapy for PD (45). However, a different study reported conflicting results as bexarotene treatment failed to protect against dopaminergic cell loss, striatum innervation, and consequently motor impairment in PD animal models with 6-OHDA and α -syn overexpression (56). Nevertheless, bexarotene treatment did restore the expression of a subset of Nurr1 target genes, including GDNF and the receptor kinase Ret. Recently, it was shown that treatment of both α -syn overexpression and neurotoxin-lesioned PD mice models with BRF110, a synthetic molecule that is able to activate Nurr1 specifically through RXR α , exerted neuroprotective effects (57). Similarly, IRX4204, another synthetic drug that activates Nurr1 through RXR binding, prevented a PD-like phenotype at the molecular, cellular, and behavioral levels in the 6-OHDA rat model (58). These reports support the potential value in exploring Nurr1:RXR α activation as a therapeutic approach for PD.

2.3. RXR in Huntington's Disease

RXR isoform expression seems to be differentially regulated in the frontal cortex and caudate of HD patients, although an increase in RXR α is the most consistent change in these brain regions (Table 2). Recently, the RXR agonist bexarotene was shown to be neuroprotective when administered to the HD mouse model N171–82Q, rescuing the HD neurological phenotype and significantly extending the survival of these animals (59). Since RXR agonists are able to dimerize with different NRs, the authors proposed that bexarotene exerts its salutary effects by inducing the formation of an RXR:PPAR β/δ heterodimer. This heterodimer activates a specific genetic program that subsequently restores altered neuronal mitochondrial function and protein quality control in HD, leading to neuroprotection. Although a PPAR β/δ -specific ligand elicited a similar range of neuroprotective effects (60), it is important to note that RXR activation by bexarotene leads to the activation of several different genetic programs regulated by distinct NRs; hence, it is likely that PPAR β/δ is not the only receptor playing a role in this bexarotene effect.

2.4. RXR in Amyotrophic Lateral Sclerosis

Among the RXR isoforms there is a selective decrease of RXR γ mRNA levels in the spinal cords of ALS patients (Table 2). Treating the ALS mouse model SOD1^{G93A} with the RXR agonist bexarotene attenuated the impaired motor function and weight loss, and increased survival by 30 % (61). The authors suggested that bexarotene exerted a neuroprotective effect on motor neurons by preserving synapses and reducing reactive astrogliosis. Given the limited therapeutic options for ALS, a clinical trial of bexarotene might be warranted.

2.5. RAR in Alzheimer's Disease

Increased RAR α expression in the cortex of AD patients, possibly in both neuronal and nonneuronal cells depending on the specific cortical area (Table 2), could indicate important cell type-specific roles for this isoform in AD. The activation of this specific isoform, but not the others, is able to repress the production of A β (61) while simultaneously inducing microglial-mediated A β clearance (62), further suggesting an important role for RAR α in AD pathology. As previously mentioned, vitamin A (retinol) metabolites, such as RA and 9-*cis*-retinoic acid, are important endogenous agonists for RAR and RXR (23–25). Vitamin A deficiency has been correlated with cognitive decline in the elderly (63), and numerous studies have found lower levels of vitamin A in AD patients (Table 2). Both vitamin A deficiency and marginal vitamin A deficiency have been suggested to facilitate AD pathogenesis by increasing A β levels and deposition (63, 64), which is consistent with the observation that RXR and RARs modulate both A β clearance and production in AD animal models (49).

It has been postulated that AD pathology is linked to the lack of availability of RA in the brain, which results in a feedback activation of retinaldehyde dehydrogenase (raldh), an enzyme involved in RA synthesis from vitamin A (65). Low levels of RA could be due to vitamin A deficiency in AD (Table 2), but it has also been observed that A β is able to repress RA synthesis (62), which suggests that there are pathological mechanisms that could be responsible for decreasing RA availability in the AD brain even in the presence of normal levels of vitamin A. Overall, RA deficiency and the subsequent impairment of RAR signaling might be important mechanisms in AD pathogenesis or disease progression. Unfortunately, adverse side effects and cytotoxicity of RA at higher concentrations have restricted its clinical applications. Tamibarotene (Am80), a synthetic retinoid approved in Japan for the treatment of acute promyelocytic leukemia, is a RAR agonist with high specificity for RAR α and RAR β . Treatment of APP23 transgenic mice with Am80 lowered insoluble A β 40 and A β 42 levels by upregulating expression of α -secretase (66), and in combination with HX630, an RXR agonist, Am80 drastically enhanced the learning ability of these mice (67). Am80 has been tested in patients suffering from AD in a small phase II clinical trial (68), but the results have not yet been disclosed. Acitretin, another RAR agonist, has also been tested in a pilot phase II clinical trial for AD (69). This study demonstrated the safety and tolerability of acitretin in human patients, and also reported that this drug promotes the nonamyloidogenic processing pathway of APP. In light of these results, the authors suggest that acitretin has promising therapeutic potential and should be tested in larger and longer trials. This is an uncommon case of a clinical trial using an NR-targeted therapy that yielded promising results for a neurodegenerative disease, which warrants further clinical testing.

2.6. RAR in Parkinson's Disease

Global gene expression analysis indicates that RAR γ mRNA is increased in the striatum of PD patients (Table 2). There are no differences in serum levels of vitamin A in PD patients compared to controls (Table 2). It has been reported, however, that the transcript levels of *raldh1* are markedly lower in the nigral neurons of PD patients, and that low levels of this enzyme in dopaminergic neurons correlate with neuronal dysfunction (68). This suggests

that reduced production of RA and retinoid signaling might be involved in PD pathogenesis; however, the study of RAR as a therapeutic target for PD has been very limited. The administration of RA-loaded polymeric nanoparticles to MPTP mice has a neuroprotective effect on dopaminergic neurons (70), and the treatment of 6-OHDA mice with 9-*cis*-retinoic acid, which binds RAR even though it is an agonist of RXR, leads to neuroprotection of nigrostriatal dopaminergic neurons (71). Moreover, the RAR agonist Am80 prevents dopaminergic cell loss in the substantia nigra in mice challenged with lipopolysaccharide (72), which further suggests a potential neuroprotective role of RAR in diseases such as PD.

2.7. RAR in Huntington's Disease

RAR β seems to be the only RAR isoform that exhibits abnormal expression in the brain of HD patients, as evidenced by reduced mRNA levels in the caudate (Table 2). Notably, the *raldh1a1* transcript level is increased in the caudate of HD patients (73). Although vitamin A levels in HD patients have not been reported, one could speculate that this increase in *raldh1a1* might be a compensatory mechanism for reduced vitamin A levels, analogous to what occurs in AD. The potential therapeutic role of RAR activation has not been explored in HD; however, it was recently reported that RAR β target genes are particularly affected in HD, which is thought to be due to sequestration of RAR β in htt protein aggregates (74). Hence, RAR β activation could be therapeutically relevant in HD.

2.8. RAR in Amyotrophic Lateral Sclerosis

RAR α and RAR γ transcript levels are downregulated in spinal cord motor neurons from ALS patients (Table 2). Conversely, the nuclear levels of RAR β are reported to be increased in motor neurons of sporadic ALS patients, suggesting higher activity (Table 2), which is proposed to be neuroprotective since increased RAR β activity is antiapoptotic and protects motor neurons from oxidative-induced cell death (75). It has been hypothesized that a defect in retinoid signaling could be a key factor in ALS pathogenesis. In spinal cord motor neurons from ALS patients, the expression of *Raldh2*, an enzyme that produces RA, is decreased (76), which suggests that there might be a depletion of retinoid ligands in spite of no changes in vitamin A levels, similar to what has been reported in PD (Table 2). The subsequent reduction in retinoid signaling could play an important role in disease progression. These data suggest that RARs could be a potential therapeutic target for ALS; however, the administration of RA to the ALS mouse model SOD1^{G93A} was found to decrease the life span of the animals, although this effect was not due to an exacerbation of the pathology (77). In a small pilot trial, the treatment of ALS patients with RA and pioglitazone as an add-on to the traditional riluzole therapy did not delay disease progression (78). Nonetheless, the limitations of this study confound interpretation of the data, specifically the relatively small size of the trial, in which a significant number of patients discontinued RA due to their inability to tolerate its side effects, and the fact that all subjects started with a three-drug regimen.

2.9. LXR in Alzheimer's Disease

Since LXR expression is not greatly affected in AD (Table 2), the availability of endogenous ligands might be a crucial factor that dictates LXR activity. A recent study reported that the levels of several oxysterols, including well-characterized LXR agonists, exhibit an abnormal

profile in the brain of late-stage AD patients (Table 2). Specifically, 27-hydroxycholesterol (27 OHC) and 25-hydroxycholesterol (25OHC) levels were found to be increased and the levels of 24S-hydroxycholesterol (24OHC) decreased. Moreover, desmosterol, another endogenous ligand of LXR, is also decreased in the AD brain (Table 2). Hence, it is not clear if the overall balance between the levels of LXR agonists in the AD brain would result in increased or reduced LXR activation. It is important to consider that desmosterol inhibits inflammatory gene expression, in part, through LXR-dependent mechanisms (79). A decrease in the LXR-mediated anti-inflammatory response in the AD brain due to reduced levels of desmosterol could be a relevant mechanism in AD pathogenesis or progression. Many studies have reported beneficial effects of different LXR ligands, with several animal models of AD showing a decreased A β burden and improved cognitive function. The underlying mechanisms are diverse, including modulation of neuronal function, A β degradation, anti-inflammatory mechanisms (3, 49), and the restoration of microvasculature architecture, which decreases A β deposition in blood vessels (80). It is still not clear to what extent the therapeutic roles of LXR α and LXR β isoforms differ in neurodegenerative diseases; however, the development and utilization of isoform-selective agonists could shed some light on that subject. Since LXR β activation, in contrast to LXR α , does not seem to induce hepatic steatosis, the side effects generally associated with LXR agonists could also be addressed by the use of isoform selective ligands (81).

2.10. LXR in Parkinson's Disease

Similar to AD, both LXR α and LXR β transcript levels do not seem to change in the striatum and substantia nigra of the brains of PD patients (Table 2). The plasma levels of 24OHC and 27 OHC are similar in PD patients and controls, but 10% of a cohort of PD patients exhibited an increase in both of these oxysterols in the CSF (Table 2). The levels of 27OHC are particularly relevant in PD since it has been reported that 27OHC increases the levels of α -syn in human neuroblastoma cell lines through LXR β , suggesting a deleterious effect on dopaminergic neurons in PD (82–84). On the other hand, the synthetic LXR agonist GW3965 exerts a neuroprotective effect in the MPTP PD mouse model by reducing the glial inflammatory response (85). Nonetheless, the role of LXR β in an acute insult model, such as MPTP-lesioned mice, may greatly differ from its role in the context of a chronic progressive pathology.

2.11. LXR in Huntington's Disease

In HD patients, transcriptomic analysis reveals that LXR α expression is increased in the caudate and LXR β expression is decreased in the cerebellum (Table 2). It has been reported that wild-type htt acts as an LXR cofactor and that mhtt loses this function, thereby reducing the transcriptional activity of LXR and the expression of its target genes (86). Additionally, mhtt reduces ApoE secretion and cholesterol transport from astrocytes to neurons, leading to neuronal dysfunction, due to reduced expression of the LXR targets ABCA1 and ApoE in astrocytes (87,88). HD patients exhibit reduced levels of 24OHC in the putamen and caudate, while 27OHC and desmosterol are increased in the caudate (Table 2). Although the expression profile of LXR isoforms is not consistent across HD brain regions, the decrease in 24OHC is consistent with repression of the LXR pathway in glial cells, since 24OHC has been proposed to be an important regulator of the cholesterol shuttle from astrocytes to

neurons (89). This reduction of 24OHC is also observed in the CSF of several HD mouse models (87). The lack of LXR signaling, due to the interaction of this receptor with mhtt, and reduced levels of the LXR ligand 24OHC are likely to reduce cholesterol transport to neurons, which will very likely affect neuronal function and disease progression. Treatment of the R6/2 murine model of HD with cholesterol-loaded nanoparticles rescued synaptic dysfunction and cognitive deficits (90), which could be due to a compensation for the lack of LXR-mediated cholesterol transport. The treatment of R6/2 brain slices with the LXR agonist T0901317 reversed the abnormal electrophysiological profile observed in these mice (91). The same compound is able to partially rescue the phenotype of zebrafish lacking huntingtin (86). These studies suggest that LXR activation might be a promising therapeutic approach for HD.

2.12. LXR in Amyotrophic Lateral Sclerosis

Global gene expression analysis of motor neurons obtained from the spinal cord of sporadic ALS and control patients suggests that neuronal LXR expression does not change in ALS (Table 2). Hence, the levels of endogenous ligands may strongly dictate the activation status of these NRs. Although the CSF levels of desmosterol seem to be elevated in ALS patients compared to control samples, it is not clear how the levels of 24OHC and 27OHC change (Table 2). The CSF and serum levels of 25OHC are increased in ALS patients (Table 2), and serum levels of 25OHC are positively correlated with disease severity and progression (92). Based on in vitro results, these authors suggested that 25OHC is implicated in ALS progression by eliciting neurotoxic effects through activation of LXR in neurons. Although activation of LXR seems deleterious in this context, the lack of LXR β in mice leads to the adult onset of an ALS-like motor neuron pathology (93). This apparent discrepancy might be related to the signaling of LXR in different cell types or even to the differences in signaling between LXR isoforms.

2.13. PPARs in Alzheimer's Disease

The analysis of several transcriptomic data sets suggests that the expression of the PPAR isoforms remains unchanged in the brain of AD patients compared to controls (Table 2). However, a comparison between AD patients in different Braak stages revealed decreased mRNA expression of PPAR α and PPAR β/δ and increased PPAR γ expression in the brain throughout AD progression (94). The levels of several PUFA PPAR ligands, including DHA, are increased or decreased depending on the brain region (Table 2). Some of these changes in PUFA levels exhibit a significant correlation with disease progression in terms of neurofibrillar pathology, amyloid plaque burden, and cognitive decline (95). Furthermore, DHA and DHA-derived metabolites are able to specifically activate PPAR γ , which leads to an inhibited inflammatory response and reduced A β production in animal models of AD (96, 97); in light of these findings, it has been suggested that dietary intake of DHA could reduce the risk of AD (98). Several epidemiological studies have reported that treatment with nonsteroidal anti-inflammatory drugs reduces the risk of AD, possibly due to their ability to activate PPAR γ (99), and the treatment of diabetic patients with the PPAR γ agonist pioglitazone reduces the risk of dementia by 47% (100). These findings support the idea that compromised PPAR γ signaling might be involved in AD pathogenesis. The increase in PPAR γ expression as AD progresses might result from a feedback mechanism

that boosts PPAR γ signaling and controls inflammation. PPAR ligands seem to be beneficial in several experimental animal models of AD. Treatment of AD mouse models with pan-PPAR agonists or agonists for specific PPARs isoforms leads to a decrease in A β burden, p-tau, and inflammation, accompanied by an overall improvement of behavioral outcomes. The mechanisms underlying these PPAR effects seem to be related to A β production and clearance, neuronal function, anti-inflammatory mechanisms, and mitochondrial function (49, 101). The PPAR γ agonist pioglitazone was recently described as being effective in reversing the A β -induced blood-brain barrier dysfunction in APP mice, rescuing the expression of several proteins involved in a variety of functions, including cerebrovascular vasoconstrictive tone and vascular compliance (102). A phase III study of pioglitazone, initiated by Takeda and Zinfandel Pharmaceuticals, is currently underway and is estimated to be completed in 2019. However, rosiglitazone, another PPAR γ agonist, has shown no clinical efficacy in three phase III trials (103, 104).

2.14. PPARs in Parkinson's Disease

The mRNA expression of all PPAR isoforms does not seem to change in the striatum and substantia nigra of PD patients compared to controls (Table 2). A significant decrease in the levels of several PUFA PPAR ligands has been reported in the anterior cingulate cortex, a region that shows accumulation of α -syn in PD (Table 2). In the occipital cortex, a region largely devoid of pathology, the levels of PUFAs are similar between PD and control samples (Table 2), suggesting that the changes in PUFAs are likely related to the pathophysiology of PD. Interestingly, in vitro evidence indicates that α -syn decreases PPAR γ expression and signaling, which can be rescued by overexpressing PPARs or RXR α (105). A retrospective cohort study revealed that diabetic patients who were prescribed the PPAR γ agonists rosiglitazone or pioglitazone exhibited a reduced risk of PD onset (106). These findings support the idea that inactivation of PPAR signaling in PD, specifically PPAR γ , due to the lack of endogenous ligands and/or interaction with α -syn possibly contributes to PD pathogenesis and progression. Several studies have shown that various PPAR isoform agonists are neuroprotective in animal models of PD (107–111). Recently, pioglitazone was shown to exert its neuroprotective effects by facilitating hippocampal neurogenesis in 6OHDA-lesioned rats (112). Rosiglitazone was also found to be neuroprotective in PD animal models, primarily by rescuing mitochondrial function and inducing the expression of antioxidative enzymes (107, 113). Despite the promising preclinical data and a good pharmacological profile, clinical trials using PPAR agonists have failed. A recent clinical trial concluded that pioglitazone is unlikely to be an effective intervention to slow disease progression in early PD and recommends that it should not be considered for further study (114).

2.15. PPARs in Huntington's Disease

In HD patients, the pattern of PPAR expression is isoform and region specific, and plasma levels of fatty acids remain unaltered relative to controls (Table 2). Recently, it has been shown that mhtt interacts not only with LXR but also with the PPAR β/δ isoform and represses transactivation (60). Although PPAR β/δ expression levels do not change in the brains of patients (Table 2), the PPAR β/δ pathway is likely to be inhibited in the HD brain, especially in areas that accumulate mhtt. Treatment of the HD mouse model R6/2 with the

pan-PPAR agonist benzaifibrate served a neuroprotective function, reduced HD neuropathologic features, and increased mitochondrial density in the striatum of these animals (115). Furthermore, the treatment of R6/2 mice with the PPAR γ agonist rosiglitazone reversed motor deficits and weight loss and reduced htt aggregates, although there was only a modest increase in survival (116). The activation of PPAR γ with rosiglitazone in the HD mouse model N171–82Q significantly improved motor function (117). The mechanisms underlying this protective effect of PPAR γ in HD seem to be related to rescuing compromised mitochondrial function in HD, an increase in mechanisms that protect from oxidative stress, and preventing BDNF depletion (117, 118). Treatment of the HD mouse models BAC-HD97 and N171–82Q with the PPAR β/δ agonist KD3010 rescued the HD neurological phenotype, conferred neuroprotection, and extended survival (60). The underlying mechanism for the beneficial effects of PPAR β/δ in HD animal models, similar to PPAR γ , seems to involve the rescuing of neuronal mitochondrial function. These preclinical results are very promising and support the idea of using this therapeutic strategy in future clinical trials for HD.

2.16. PPARs in Amyotrophic Lateral Sclerosis

In motor neurons obtained from the spinal cords of ALS patients, the transcript levels of PPAR isoforms do not change when compared to controls (Table 2). Nonetheless, DHA levels in the spinal cords of ALS patients are reduced (Table 2). The dietary intake of PUFAs, including DHA, has been correlated with a decreased risk or delayed onset of ALS (119, 120). In light of these findings, one could hypothesize that a reduction in PPAR activation in the spinal cord motor neurons of ALS, due to lack of endogenous ligands, could contribute to disease pathogenesis or progression. Treatment of the ALS mouse model SOD1^{G93A} with the PPAR γ agonist pioglitazone was neuroprotective and led to a decrease in inflammation, improved motor behavior, and extended survival (121, 122). In a recent screening of 1,200 US Food and Drug Administration–approved compounds, pioglitazone was identified as a neuroprotective agent in *Drosophila* ALS models. The treatment of the TDP-43 *Drosophila* ALS model with pioglitazone attenuated neuronal loss and mitigated motor dysfunction, although there was no increase in life span (123). These authors also demonstrated that pioglitazone is neuroprotective in an FUS, but not a SOD1^{G93A}, *Drosophila* model. One of the proposed mechanisms underlying the beneficial effects of PPAR γ in ALS is related to its role in the defense against lipid peroxidation by inducing the expression of lipid detoxification enzymes, such as lipoprotein lipase and glutathione *S*-transferase α -2 (124). Administration of fenofibrate, a pan-PPAR agonist to SOD1^{G93A} mice, elicited a significant delay in disease onset and progression, as well as prolonged survival of treated mice (125). The authors proposed that the neuroprotective properties of fenofibrate are related to a reduction in neuroinflammation and the protection of mitochondrial integrity. These encouraging findings suggest that PPAR is a promising drug target in ALS. However, a clinical trial using pioglitazone as an add-on therapy to riluzole reported that pioglitazone has no beneficial effects on the survival of ALS patients (126). Another trial also showed that pioglitazone treatment failed to alter clinical disease progression over a 6-month period in patients taking riluzole and tretinoin (78).

2.17. Nurr1 in Alzheimer's Disease

Although mRNA levels of Nurr1 were reported to be elevated in neurons of specific brain regions in AD, there seems to be a decrease in Nurr1 protein expression, particularly in neurons affected by p-tau aggregates (Table 2), suggesting that there might be region- and cell type-specific regulation of Nurr1 expression in AD.

2.18. Nurr1 in Parkinson's Disease

There is a decrease in Nurr1 protein expression that appears to be selective to the substantia nigra and specifically to nigral neurons that contain α -syn inclusions (127). This observation is in line with another study reporting that α -syn is able to reduce Nurr1 expression in nigral dopaminergic neurons in rats (40). The activation of Nurr1 using ligands for RXR is a promising strategy for PD, and a different class of drugs that activate Nurr1 through physical interaction with its ligand binding domain has also shown neuroprotective properties in PD models. The antimalarial drugs amodiaquine and chloroquine interact with the Nurr1 ligand binding domain and stimulate its transcriptional activity. This activation leads to a Nurr1-mediated increase in transcriptional activation of dopaminergic-specific genes in neurons and the transrepression of neurotoxic proinflammatory gene expression in microglia. This dual mechanism was proposed to be responsible for the significant improvement in behavioral deficits in the 6-OHDA rat model of PD that was treated with amodiaquine (128).

3. CONCLUSIONS AND FUTURE PERSPECTIVES

3.1. Experimental Models and Design

An extensive body of evidence has established that NR activation exerts a beneficial effect in preclinical animal models of neurodegenerative diseases. However, as Section 2 highlights, the translation of this therapeutic strategy to the clinic has not yet been successful. One possible reason could be related to the fact that the current animal models do not truly recapitulate human biology and pathology in all its complexity. Furthermore, the stage of the disease in which the model animals are treated with NR agonists could also be a critical determinant. In many studies, the treatment of these animal models starts significantly before they exhibit neuronal loss and cognitive or motor deficits, which therefore does not correspond to the symptomatic stage of patients when starting medication. In essence, many of the treatment paradigms used in a vast number of animal studies are more analogous to a prevention strategy rather than a treatment strategy. This could contribute to the failure of translation into clinical practice, as the activation of particular NRs might only be effective at very early stages of disease, or merely as a prevention strategy, and not in patients with advanced symptomatic pathologies. This rationale could explain why the epidemiological studies demonstrating a reduced risk for neurodegenerative diseases in people taking PPAR agonists for other indications are in agreement with several studies using animal models, while later-stage clinical trials fail to demonstrate the efficacy of this type of drug. Overall, the different biology of animal models compared to humans is an unavoidable limitation that will account for translational limitations; however, the stage of disease progression at which researchers start treatment of these animals should be carefully determined, taking into account clinical practice in human patients. This might be a crucial detail in the study design

that could dictate the translational success of a particular therapeutic strategy. Another key factor to consider is the peripheral impact of NR agonists, especially with respect to adverse effects. This can be circumvented by designing selective agonists for particular NR isoforms, using targeted strategies for drug delivery, adjusting the dosage, or using combination therapies with drugs that mitigate the peripheral side effects. Taking these concerns into consideration when designing experiments in animal models will increase the chance of a successful translation to clinical trials.

3.2. Novel Research Avenues

The analysis of different experimental data sets and human studies suggests that each neurodegenerative disease exhibits its own distinct pattern of NR dysfunction. Indeed, the activation of some NRs, such as LXR, might be detrimental in particular diseases, such as PD or ALS (82–84, 92), and beneficial in others. Hence, novel therapeutic strategies involving NRs might need to be specific for each disease. However, as highlighted in Sections 2.5–2.8, the gene expression analysis of human patients suggests that the repression of RA synthesis, which leads to a reduction of retinoid signaling through RAR, might be a common mechanism involved in the pathogenesis or disease progression of AD, PD, HD, and ALS (Figure 3). This idea is supported by several preclinical and a few clinical studies using synthetic agonists for RAR, highlighted in Sections 2.5 and 2.8. Although this latter strategy has already shown promising results in both preclinical and some clinical studies, it is a very targeted approach to RARs. Thus, it might not fully reestablish the endogenous roles of RA in the brain, such as the regulation of RARs activation patterns in specific cell types or brain regions that synthetic agonists may not be able to recapitulate and also other endogenous roles not directly related to NRs. An alternate strategy to address this retinoid deficit could be to restore the levels of RA synthesis in the affected areas by activating the synthesis pathway, which seems to be compromised in these diseases. The inhibition of RA catabolism by inhibiting the retinoic acid 4-hydroxylase (CYP26) could also be a promising approach (Figure 3). Additionally, this strategy would restore not only RAR signaling but also other NR pathways, including PPAR, Nurr1, and LXR. Indeed, RA has been shown to activate PPAR β/δ (129), maintain Nurr1 expression in a PD mouse model (130), and induce the LXR target gene *ABCA1* in macrophages (131). Overall, the restoration of RA homeostasis might be a very promising therapeutic approach for several neurodegenerative diseases, as it seems to be a common feature across these disorders.

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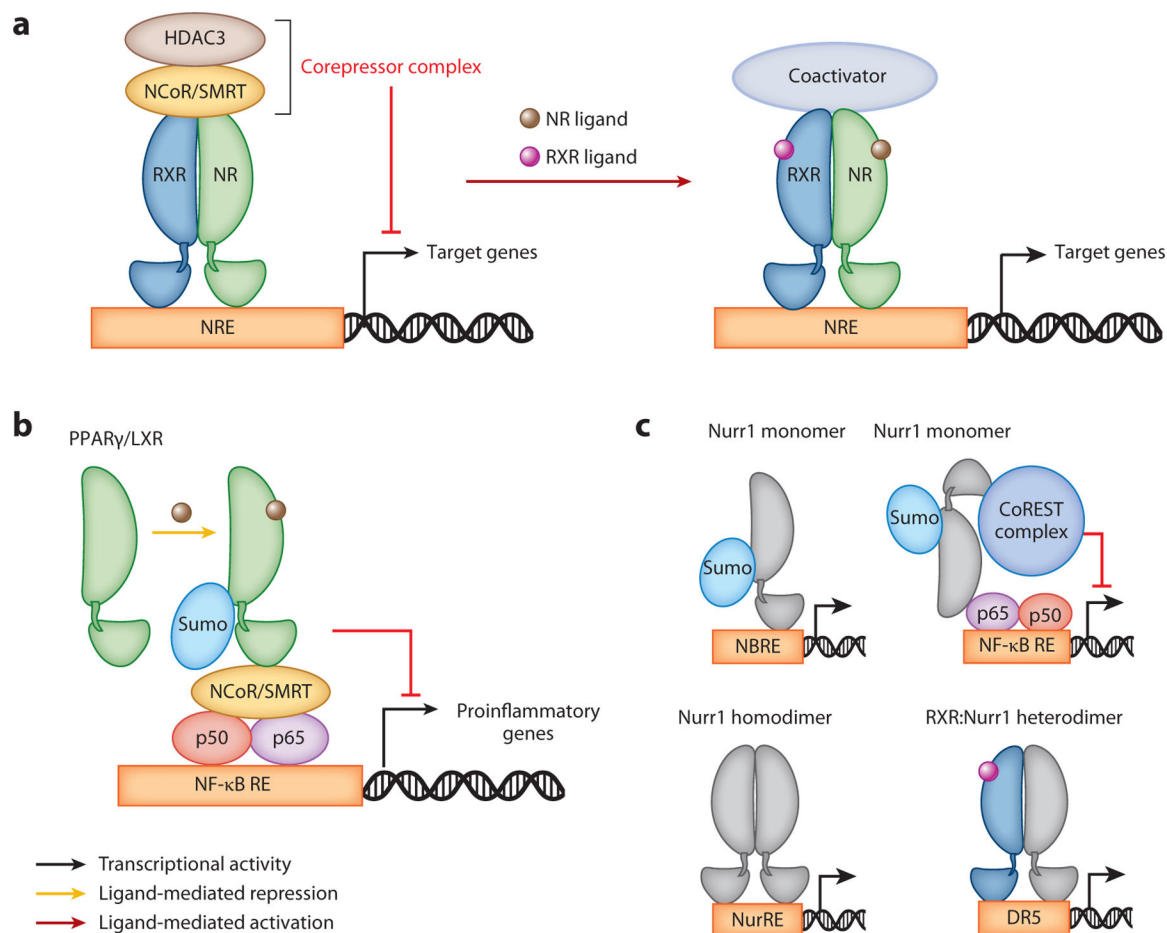
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**Figure 1.**

NR mechanisms of action. (a) NRs of the type II family, namely RARs, LXRs, and PPARs, bind to DNA-specific NRE within the promoters of their target genes as obligate heterodimers with RXR and regulate gene expression. In the absence of ligand binding, these NR heterodimers associate with corepressor complexes such as NCoR/SMRT and HDAC3, which results in the repression of target genes. Conformational changes upon binding of NR ligands result in the dismissal of the corepressor complex and the association of NRs with coactivators, resulting in the transcriptional activation of target gene expression. (b) NR monomers such as PPAR γ or LXR can undergo sumoylation upon ligand binding and recruit a NCoR/SMRT corepressor complex inhibiting gene expression, such as NF- κ B-regulated proinflammatory genes. (c) Unlike RARs, PPARs, and LXRs, Nurr1 can directly bind to response elements not only as RXR:Nurr1 heterodimers but also as monomers or homodimers and activate target genes. Nurr1 homodimers bind to NurRE, while RXR:Nurr1 heterodimers bind to DR5. Sumoylation of Nurr1 leads to monomerization, and these monomers can activate NBRE, or interact with p50 on NF- κ B RE and recruit the corepressor CoREST, inhibiting the expression of NF- κ B-regulated proinflammatory genes. Abbreviations: CoREST, REST corepressor; DR5, direct repeats separated by five nucleotides; HDAC3, histone deacetylase 3; LXR, liver X receptor; NBRE, NGFI-B responsive elements; NCoR, nuclear receptor corepressor; NF- κ B, nuclear factor- κ B; NF-

κ B RE, NF- κ B response elements; NR, nuclear receptor; NRE, nuclear receptor response elements; Nurr1, nuclear receptor related-1 protein; NurRE, Nur response element; PPAR, peroxisome proliferator-activated receptor; RAR: retinoic acid receptor; RXR, retinoid X receptor; SMRT, silencing mediator of retinoid and thyroid hormone receptors. Original and modified images from somersault:1824 (<http://www.somersault1824.com>).

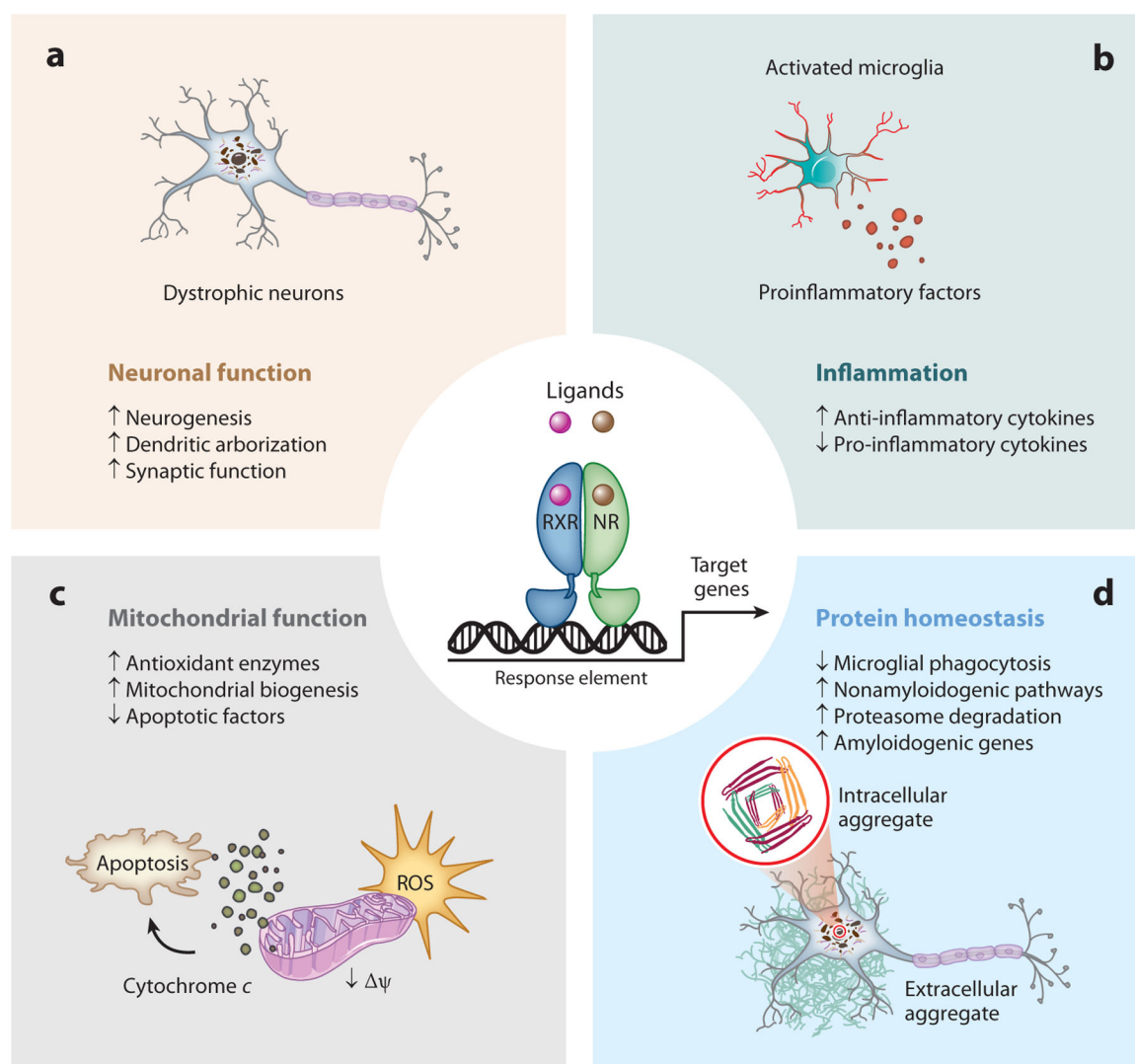


Figure 2.

NR activation in neurodegenerative diseases. Several natural and synthetic ligands of NRs exert beneficial effects in different neurodegenerative disease models. The activation of NRs counteracts pathological mechanisms that are common across neurodegenerative diseases, such as inflammation and neuronal dysfunction, and rescues several compromised biological functions, including mitochondrial function and protein homeostasis. The beneficial effect of NR ligands in neurodegenerative diseases relies on the combination of the different mechanisms. (a) NRs exert a neuroprotective effect by stimulating neurogenesis, dendritic arborization, and synaptic function. (b) Neuroprotection is also a consequence of other mechanisms, including a decrease in microglia activation and inflammation. (c) Additionally, NR activation preserves the mitochondrial function and the induced anti-oxidative machinery, reducing the production of ROS and apoptosis. (d) NRs have also been known to regulate the production of pathological proteins and stimulate the clearance of aggregates of these proteins, such as A β . Abbreviations: NR, nuclear receptor; ROS, reactive oxygen species; RXR, retinoid X receptor. Original and modified images from somersault: 1824 (<http://www.somersault1824.com>).

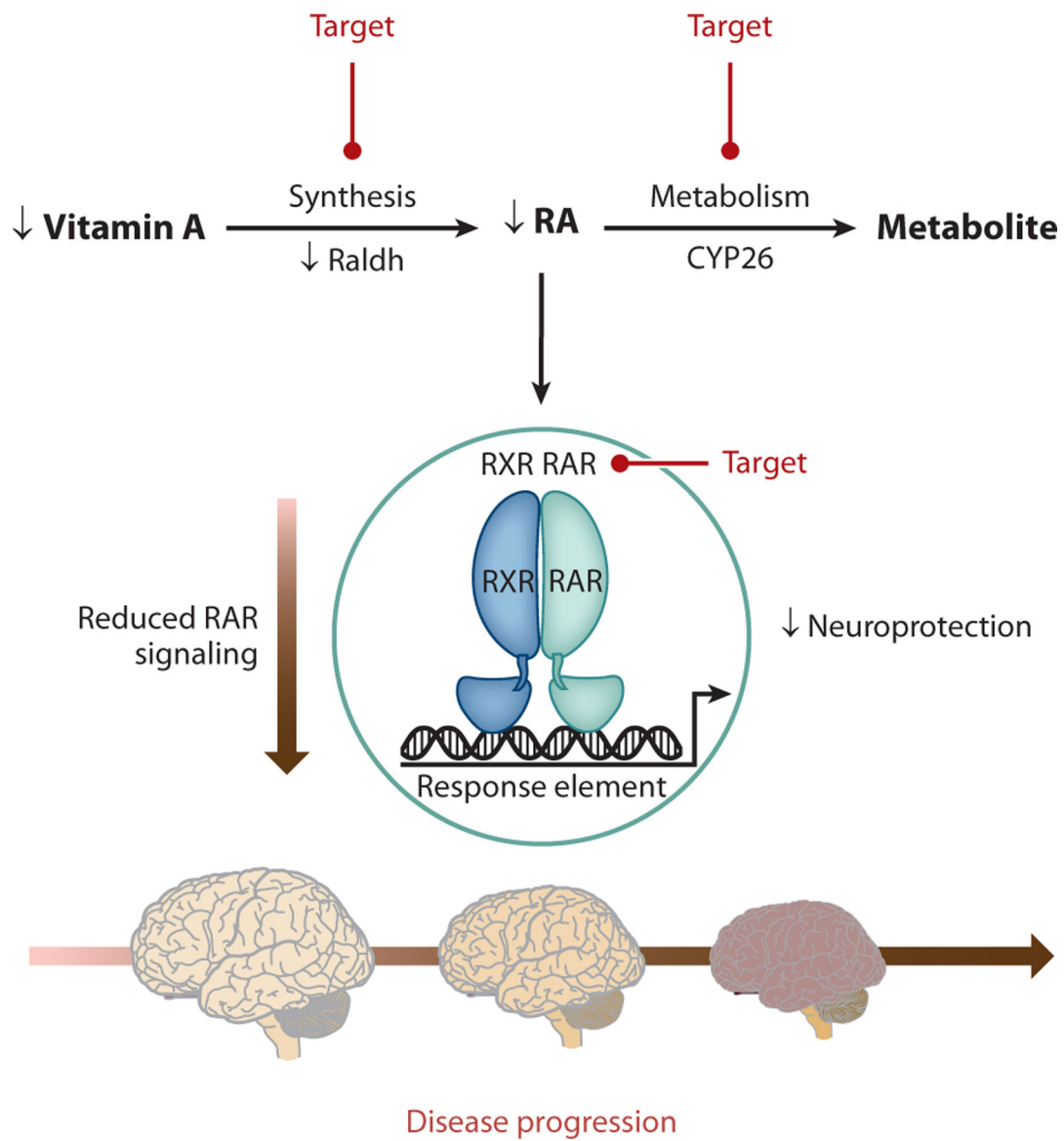


Figure 3.

RAR signaling deficiency in the progression of neurodegenerative diseases. Several lines of evidence suggest that RAR activation mediates neuroprotection in the context of neurodegenerative diseases, and the lack of RAR signaling could play a major role in the progression or pathogenesis of this type of disorder. Across several neurodegenerative diseases, there is evidence that points to a reduction in the availability of RA, the endogenous RAR ligand, which could underlie the repression of RAR activation in the brain. Considering the analysis of tissue from patients, this reduced RA availability could be due to low levels of its precursor, vitamin A, but also because of a reduced expression of the enzymes responsible for its synthesis, such as Raldh. Therefore, therapeutic strategies aimed at particular targets (*red dots*) to normalize retinoid signaling, such as the activation of enzymes responsible for RA synthesis, the inhibition of RA metabolism, or directly activating RAR with synthetic agonists, may be of utility. Abbreviations: CYP26, retinoic

acid 4- hydroxylase; RA, all-*trans*-retinoic acid; Raldh, retinaldehyde dehydrogenase; RAR, retinoic acid receptor; RXR, retinoid X receptor. Original and modified images from somersault:1824 (<http://www.somersault1824.com>).

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Table 1

Ligands of nuclear receptors that exhibit beneficial effects in preclinical models of neurodegenerative diseases, and their current status in clinical trials

Nuclear receptors	Ligands	Disease	Models	Clinical trials	References
RXR	Bexarotene	AD	Genetic models: 5XFAD, APP/PS1, APP/PS1-21, Tg2576 mice	Pilot trial: no clinical benefit	47, 49, 54, 55
		PD	Toxin-induced neurotoxicity: 6-OHDA rats	None	45
		HD	Genetic models: N171-82Q mice	None	60
		ALS	Genetic models: SOD1 ^{G93A} mice	None	61
	BRF110	PD	Toxin-induced neurotoxicity: MPTP and 6-OHDA mice	None	57
	IRX4204	PD	Toxin-induced neurotoxicity (in vivo): 6-OHDA rats	Phase 1: no results posted	58 ^a
RAR	Tamibarotene (Am80)	AD	Genetic models: APP23 mice	Phase 2: no results posted	66 ^b
	Acitretin	AD	Genetic models: APP/PS1-21 mice	Phase 2: acitretin drives nonamyloidogenic APP processing in human patients	69, 132
	RA-loaded polymeric nanoparticles	PD	Toxin-induced neurotoxicity: MPTP mice	None	70
	9- <i>cis</i> -retinoic acid	PD	Toxin-induced neurotoxicity (in vivo): 6-OHDA rats	None	71
LXR	TO901317	AD	Genetic models: Tg2576, APP23, APP/PS1, 3xTg mice	None	49
	GW3965	AD	Genetic models: Tg2576, APP23, APP/PS1, 3xTg mice	None	49
	GW3965	PD	Toxin-induced neurotoxicity: MPTP mice	None	85
PPARs	Pioglitazone	AD	Genetic models: Tg2576, 5XFAD, APP/PS1, 3xTg, APPV7171 mice and several others	Phase 2: no efficacy demonstrated on clinical outcomes	49, 101, 133
		PD	Toxin-induced neurotoxicity: MPTP, 6-OHDA rodents	Phase 2: unlikely to modify disease progression	107-109, 112, 114
		ALS	Genetic models: SOD1 ^{G93A} mice, TDP and FUS <i>Drosophila</i>	Pilot trial: failed as an add-on to riluzole and tretinoin therapy	78, 121-123, 126

Nuclear receptors	Ligands	Disease	Models	Clinical trials	References
				Phase 2: failed as an add-on to riluzole therapy	
	Rosiglitazone	AD	Genetic models: Tg2576, 5XFAD, APP/PS1	Phase 3: fail as monotherapy in cognition or global function Phase 3: fail as an add-on to acetylcholine esterase inhibitor	49, 101, 103, 104
		PD	Toxin-induced neurotoxicity MPTP, 6-OHDA animals	None	107, 108
		HD	Genetic models: N171–82Q, R6/2 mice	None	117, 118
	Genistein	AD	Hippocampal injection of A β peptides in rats Genetic models: APP/PS1 mice	Phase 1: recruiting	134
Nurr1	Amodiaquine	PD	Toxin-induced neurotoxicity: 6-OHDA mice	None	128
	Chloroquine	PD	Toxin-induced neurotoxicity: 6-OHDA mice	None	128

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; HD, Huntington's disease; PD, Parkinson's disease; RA, all-*trans*-retinoic acid.

^aNCT02438215.

^bNCT01120002.

Table 2

Transcript expression patterns and ligand levels of nuclear receptors in neurodegenerative diseases

NR Isoform	Alzheimer's disease			Parkinson's disease			Huntington's disease			Amyotrophic lateral sclerosis		
	Expression	Ligands	References	Expression	Ligands	References	Expression	Ligands	References	Expression	Ligands	References
RXR α	NC cx, hp, n (dg) \uparrow (tg, hp) ^a	\downarrow Retinol (serum)	135–142	\downarrow dopaminergic n NC st, sn	NC Retinol (serum)	139, 143–145	\uparrow fc, cd NC cb	NA	73, 146	NC sc	NC Retinol (serum)	75, 76, 147–149
RXR β	NC cx, hp			NC st, sn			\uparrow fc NC cd, cb			NC sc		
RXR γ	NC cx, hp			NC st, sn			\uparrow fc \downarrow cd NC cb			\downarrow sc		
RAR α	NC fc, hp \uparrow n-pec \downarrow ec			NC st, sn			NC fc, cd, cb			\downarrow mm-sc		
RAR β	NC cx, hp \uparrow n-pec \downarrow n-mg			NC st, sn			\downarrow cd NC fc, cb			\uparrow nuclei of mm		
RAR γ	NA			\uparrow st NC sn			NC fc, cd, cb			\downarrow mm-sc		
LXR α	NC cx, hp	\uparrow 25OHC, 27OH \downarrow 24OHC, DESM (brain)	136, 137, 150, 151	NC st, sn	NC 27OHC, 24OHC, DESM (plasma)	144, 152	\uparrow caud NC cb, fc	\downarrow 24OHC (put, cd) \uparrow 27OHC (cd) DESM (cd)	73, 146, 153	NC mm-sc	\downarrow/\uparrow 24OHC NC/ \uparrow 27OHC \uparrow DESM, 25OHC (CSF)	92, 149, 154
LXR β	NC cx, hp \uparrow n-pec			NC st, sn	\uparrow 27OHC, 24OHC (CSF 10% patients)		\downarrow cb NC (caud, fc)			NCmm-sc		
PPAR α	NC cx, hp \uparrow n-mg	\downarrow PUFAs (tg, mfg) \uparrow PUFAs (b7) \downarrow DHA (hp)	95, 136, 137, 155	NC st, sn	\downarrow PUFAs (acc) NC PUFAs (oc)	144, 156	\uparrow fc NC cb, cd	NA	73, 146	NC mm-sc	\downarrow DHA sc	149, 157
PPAR β/δ	NC cx, hp \uparrow n-mg, pec	\downarrow PUFAs (tg, mfg) \uparrow DHA (tg, mfg, b7)					NC cb, cd cb					
PPAR γ	NC cx, hp						\downarrow fc, cd NC cb					
Nurr1	NC cx, hp \uparrow n-mg, hp \downarrow niagral n ^a	NA	127, 136, 137	\downarrow niagral n ^a NC st, sn	NA	127, 144	\downarrow mc, cb NC cd, fc	NA	73, 146, 158	NC (mm-sc)	NA	149

Table shows increase (\uparrow), decrease (\downarrow), or no change (NC) in the transcript expression patterns and ligand levels of nuclear receptors in neurodegenerative diseases. Abbreviations: acc, anterior cingulate cortex; b7, Broadmann region 7; cb, cerebellum; cd, caudate; CSF, cerebrospinal fluid; cx, cortex; DESM, desmosterol; DHA, docosahexaenoic acid; fc, frontal cortex; hp, hippocampus; mfg, medial frontal gyrus; mm, motor neurons; mfg, middle temporal gyrus; n, neurons; NA, not applicable; NR, nuclear receptor; oc, occipital cortex; OHC, hydroxycholesterol; pec, posterior cingulate cortex; PPARs, peroxisome proliferator-activated receptors; PUFAs, polyunsaturated fatty acids; put, putamen; sc, spinal cord; sn, substantia nigra; st, striatum.

^aProteinexpression.